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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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LUNDGREN, JEFFREY S	
ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/762,395	GIORDANO ET AL.	
	Examiner	Art Unit	
	JEFFREY S. LUNDGREN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-141* is/are pending in the application.

4a) Of the above claim(s) *78,83-89,92-98 and 101-140* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76,77,79-82,90,91,99,100 and 141* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/14/05; 3/21/05; 11/17/06; 2/27/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Applicant's election without traverse of Group I, and the corresponding species as set forth in the Restriction Requirement of September 11, 2007, in the Reply filed on September 8, 2008, is acknowledged.

Claims 76-141 are pending in the instant application; claims 78, 83-89, 92-98, and 101-140 are withdrawn from consideration as being directed to non-elected inventions; claims 76, 77, 79-82, 90, 91, 99, 100 and 141 are the subject of the Office Action below.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on February 14, 2005; March 21, 2005; and February 27, 2007, have been considered by the Examiner. The submissions are in compliance with the provisions of 37 CFR § 1.97. Enclosed with this Office Action are return copies of the Form PTO-1449 with the Examiner's initials and signature indicating those references that have been considered.

The IDS submitted on November 17, 2006, has been considered in-part. Documents 74-556 were not considered because these documents have either not been provided, or are not available as part of the file wrapper, and have been lined through on the corresponding Form PTO-1449.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 76, 77, 79-82, 90, 91, 99, 100 and 141 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 76 and all dependent claims are indefinite for reciting the phrase "stress competent" because one of ordinary skill in the art could not reasonably determine the metes and

bounds of this limitation. The term does not appear to be a specific term of art with a well-understood and uniform meaning, nor does it appear anywhere in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 76, 77, 79-82, 90, 91, 99, 100 and 141 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for new matter. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitation "stress competent" is considered new matter because there is no reasonable description of this limitation, either literally or by way of example.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 76, 77, 79-81, 99, 100 and 141, are anticipated by Li:

Claims 76, 77, 79-81, 99, 100 and 141, are rejected under 35 U.S.C. § 102(b) as being anticipated by Li *et al.*, U.S. Patent Application Publication No. 2002/0114784 A1, published on August 22, 2002.

Claim 76 is directed towards a method of downregulating expression of a target gene in an RNA stress response-competent cell, comprising: introducing into the cell an expression vector encoding a double stranded RNA corresponding to the target gene such that said double stranded RNA is expressed and expression of said target gene is specifically downregulated,

wherein intracellular expression of said double stranded RNA in said stress response- competent cell does not induce a detectable RNA stress response.

Li teaches methods for introduction of double stranded RNA into cells, cell culture, organs and tissues, and whole organisms, particularly vertebrates, specifically attenuates gene expression (see Abstract). Regarding the particular scope of the disclosure, Li states:

> "The present invention provides a method for attenuating gene expression in a cell using gene-targeted double-stranded RNA (dsRNA). The dsRNA contains a nucleotide sequence that is essentially identical to the nucleotide sequence of at least a portion of the target gene. The cell into which the dsRNA is introduced can be derived from or contained in any organism (e.g., plant, animal, protozoan, virus, bacterium, or fungus). Gene expression can be attenuated in a whole organism, an organ or tissue of an organism, including a tissue explant, or in cell culture. Preferably, the cell is a vertebrate cell, but the invention is not limited to vertebrates. Double-stranded RNA is introduced directly into the cell or, alternatively, into the extracellular environment from which it is taken up by the cell. Inhibition is specific for the targeted gene. The targeted gene can be a chromosomal gene or an extrachromosomal gene. For example, the targeted gene may be present in the genome of the cell into which the dsRNA is introduced, or in the genome of a pathogen, such as a virus, a bacterium, a fungus or a protozoan, which is capable of infecting such cell. The targeted gene can be an endogenous gene or a foreign gene. Depending on the particular target gene and the dose of dsRNA delivered, the method may partially or completely inhibit expression of the gene in the cell. The expression of two or more genes can be attenuated concurrently by introducing two or more double stranded RNAs into the cell in amounts sufficient to attenuate expression of their respective target genes. Double stranded RNAs that are administered "concurrently" are administered, together or separately, so as to be effective at generally the same time."

Li, paragraph 0006. As noted above, Li discloses compositions and methods for in vivo and in vitro attenuation of gene expression using double stranded RNA, for example, Li teaches transforming a population of vertebrate cells with a double stranded RNA expression library, wherein at least two cells of said population of cells are each transformed with a different nucleic acid from said double stranded RNA expression library (e.g., see paragraph 53, "The ease with which dsRNA can be introduced into an intact cell or organism containing the target gene allows the present invention to be used in high throughput screening (HTS) applications"; see also

paragraph 45, "dsRNA can be supplied to a cell indirectly by introducing one or more vectors that encode both single strands of a dsRNA (or, in the case of a self-complementary RNA, the single self-complementary strand) into the cell ... Single stranded RNA is transcribed inside the cell, and, presumably, double stranded RNA forms and attenuates expression of the target gene"). Li also discloses selecting a vertebrate cell in which said nucleic acid is expressed in said cell and assaying for a modulation in the function of said cell, wherein said modulation identifies a nucleic acid that modulates the function of said vertebrate cells (e.g., see paragraph 53 wherein cell functions like cell growth and metabolism are disclosed; see also figures, especially figure 4). Finally, Lee et al. also disclose conditions that prevent and/or inhibit an interferon response (e.g., see paragraph 118, "the amount of double-stranded RNA that was used to generate the phenotypes is much less than is necessary to cause this interferon-mediated toxicity").

As in claims 76, 77 and 81, the cells of Li are considered to be "stress competent":

> "Finally, it is known that certain types of double-stranded RNA, such as mismatched or polyI/polyC RNA, can be toxic at high concentrations in eukaryotic animals (M. Kumar et al., Microbiol. Mol. Biol. Rev. 62, 1415-1434 (1998)). Although double-stranded RNA can induce interferon-.alpha./.beta. in non-immune cells, this toxicity is primarily due to an immune system response mediated through interferon production in response to viral infections. Immune system or interferon-α/β-mediated toxicity is very unlikely to play any role in generating the phenotypes we have observed. First, the phenotypes that we have generated can be observed in 24 hour embryos, long before the zebrafish immune system has been established. The thymus primordium appears in the zebrafish at approximately 54 hours, but does not enlarge significantly until 30 hours later. Rag1 and Rag2 expression cannot be detected until day 4, indicating a lack of mature T cells in the zebrafish until that time. Second, the amount of double-stranded RNA that was used to generate the phenotypes is much less than is necessary to cause this interferon-mediated cell toxicity (M. Kumar et al., Microbiol. Mol. Biol. Rev. 62, 1415-1434 (1998)). We have also found that polyl/polyC RNA can be toxic both in cultured 3T3 cells and in microinjected embryos. However, none of the ten double-stranded RNAs that we have so far examined elicit a toxic effect in vitro or in vivo. Third, the phenotypes that have been generated for each gene under study differ substantially from one another and are specifically related to the gene that was targeted. Finally, injection of control double-stranded RNA at the same concentrations does not cause a detectable deviation from the wild type expression levels or phenotype."

Li, paragraph 0118.

As in claim 80, Li teaches vertebrates (see Abstract). As in claim 79, Li teaches that the target gene is a pathogen (paragraph 0006). As in claim 90, Li teaches a decrease in target expression of at least 50%, such as 70% (paragraph 0114). As in claim 99, Li teaches detecting the effects using a microscope (see description of Figure 3). As in claim 100, the effects taught by Li include the claimed "morphological changes" such as GFP. As in claim 141, the double stranded RNA of Li is at least 20-25 nucleotides, such as Zf-T (see Figure 2B, and description thereof; see also paragraph 0039).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 76, 77, 79-82, 90, 91, 99, 100 and 141 are obvious over Fire and Wianny:

Claims 76, 77, 79-82, 90, 91, 99, 100 and 141, are rejected under 35 U.S.C. § 103(a) as being unpatentable over Fire *et al.*, WO 99/32619, published on July 1, 1999[1], and Wianny *et al.*, "Specific interference with gene function by double-stranded RNA in early mouse development" Nature Cell Biology, 2:70-75 (2000) (published on-line December, 23 1999), and optionally Li *et al.*, U.S. Patent Application Publication No. 2002/0114784 A1, published on August 22, 2002.

Claim 76 is directed towards a method of downregulating expression of a target gene in an RNA stress response-competent cell, comprising: introducing into the cell an expression vector encoding a double stranded RNA corresponding to the target gene such that said double stranded RNA is expressed and expression of said target gene is specifically downregulated, wherein intracellular expression of said double stranded RNA in said stress response- competent cell does not induce a detectable RNA stress response. The other limitations of claims 77, 79-81, 99, 100 and 141, and the corresponding teachings of Li are found in the rejection above, and hereby incorporated by reference into the instant rejection.

As in claim 76, Fire teaches a process of introducing an RNA into a living cell to inhibit gene expression of a target gene in that cell. The process may be practiced ex vivo or in vivo, and the RNA has a region with double-stranded structure. Fire teaches that inhibition is sequence-specific in that the nucleotide sequences of the duplex region of the RNA and of a portion of the target gene are identical. The present disclosure teaches that it is distinguished from prior art interference in gene expression by antisense or triple-strand methods (see Abstract). Fire teach introducing double stranded RNA into living cells to inhibit gene expression, for example, Fire teaches transforming a population of vertebrate cells with a double stranded RNA expression library, wherein at least two cells of said population of cells are each transformed with a different nucleic acid from said double stranded RNA expression library (e.g., see page 19, paragraph 1, "The ease with which RNA can be introduced into an intact cell/organism containing the target gene allows the present invention to be used in high throughput screening (HTS) ... Inserts may be derived from genomic DNA or mRNA (e.g., cDNA and cRNA) ... The amplified RNA can be fed directly to, injected into, the cell/organism containing the target gene. Alternatively, the duplex RNA can be produced by in vivo or in vitro transcription from an expression construct used to produce the library"; see also claims 1-35, especially claim 6 and page 19, line 21 of the specification wherein vertebrate "animal" and "zebra fish" cells are disclosed; see also page 28, Methods of RNA synthesis wherein "microinjection" is disclose as a transformation step; see also page 13, paragraph 2).

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[1] Alternatively, Fire et al., U.S. Patent No. 6,506,559, issued on January 14, 2003, may be used as the basis of the rejection, as this document is cumulative to WO 99/32619.

Regarding Applicants' "stress competent" limitation, Fire states that the cells may be tested for stress, and are therefore "stress competent":

> "RNA may be synthesized either in vivo or in vitro. Endogenous RNA polymerase of the cell may mediate transcription in vivo, or cloned RNA polymerase can be used for transcription in vivo or in vitro. For transcription from a transgene in vivo or an expression construct, a regulatory region (e.g., promoter, enhancer, silencer, splice donor and acceptor, polyadenylation) may be used to transcribe the RNA strand (or strands). Inhibition may be targeted by specific transcription in an organ, tissue, or cell type; stimulation of an environmental condition (e.g., infection, stress, temperature, chemical inducers); and/or engineering transcription at a developmental stage or age."

Fire, Detailed Description of the Invention.

Fire also discloses selecting a vertebrate cell in which said nucleic acid is expressed in said cell and assaying for a modulation in the function of said cell, wherein said modulation identifies a nucleic acid that modulates the function of said vertebrate cells (e.g., see page 19, paragraph 1, "Solutions containing duplex RNAs that are capable of inhibiting the different expressed genes can be placed into individual wells positioned on a microtiter plate as an ordered array, and intact cells/organisms in each well can be assayed for any changes or modifications in behavior or development due to inhibition of target gene activity"; see also Tables 1-2 and page 29, Methods for analysis of phenotypes section providing various examples of the phenotypes, "Features analyzed included movement, feeding, hatching, body shape, sexual identity, and fertility"; see also page 18, lines 11-16). As in claim 82, Fire teaches the inverted repeat (see double T7 in Figure 5A).

Wianny is directed to the study of specific interference of a given gene's function through the use of dsRNA, specifically, early mouse development. Wianny states:

> "Here, we show that dsRNA is effective as a specific inhibitor of the function of three genes in the mouse, namely maternally expressed c-mos in the oocyte and zygotically expressed E-cadherin or a GFP transgene in the preimplantation embryo. The phenotypes observed are the same as those reported for null mutants of the endogenous genes. These findings offer the opportunity to study development and gene regulation in normal and diseased cells."

Wianny, Abstract.

Wianny teaches the use of conditions that will prevent or inhibit an interferon response in animal cells (e.g., see page 73, column 2, paragraph 2, "Thus it appears that the concerns that RNAi might not work in the mouse may have been raised prematurely ... The presence of extremely low concentrations of dsRNA in viral infections triggers the interferon response ... The consequence [of this response are] a global suppression of translation, which in turn triggers apoptosis. However, we have shown here [using our conditions] that the injection of a dsRNA ... does not cause a general translational arrest [i.e., no interferon response that would otherwise lead to apoptosis], because embryos continue to develop and we see no signs of cell death"). Regarding claim 91, through routine experimentation, one of ordinary skill in the art could have reasonably optimized target gene regulation based on any of the references.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Fire, Wianny and Li are all directed to the use of dsRNA for modulating/inhibiting the expression of a target gene. It would have been obvious to one skilled in the art at the time the invention was made to screen dsRNAi as taught by Fire using the conditions as taught by Wianny because Wianny teach that their conditions can be used for the same purpose. Furthermore, one of ordinary skill in the art would have been motivated to combine the references because Wianny explicitly state that their experimental conditions can be used to overcome problems associated with RNAi screening of animal cells (i.e., prevent and/or inhibit an interferon response that would lead to cell death; see Wianny, page 73, column 2, paragraph 2), which is a preferred embodiment of Fire (e.g., see Fire, claim 6). Finally, one of ordinary skill in the art would have also reasonably expected to be successful because both Wianny and Fire show successful examples of RNAi screening using both in vivo and in vitro techniques. Therefore, the invention as a whole was prima facie obvious at the time it was invented.

Common Ownership of Claimed Invention Presumed

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Conclusions

No claim is allowable.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey S. Lundgren/
Patent Examiner, Art Unit 1639